REMARKS

Claims 1 – 36 are pending. Claims 1 – 19 and 23 – 31 have been withdrawn. No claims have been cancelled. Claims 20 and 34 have been amended. No new claims have been added. No new matter has been added. Support for the amendment to claim 34 can be found in the specification, for example at p. 30 – 31. Applicant requests entry of the amendments and reconsideration and allowance of the claims.

The Examiner indicates that claims 32 and 33 are allowable. The Examiner indicates that claim 36 is free of the prior art.

Any cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s). Favorable reconsideration in light of the remarks which follow is respectfully requested.

Information Disclosure Statement

The Examiner indicates that Applicants Information Disclosure Statement filed August 9, 2006 is acknowledged.

Drawings

The Examiner indicates that the drawings filed on August 9, 2006 are acknowledged. The Examiner has objected to the drawings because "the description of the drawings indicates that such materials may very well be critical to determining whether there exits adequate description and enablement of the instant invention." (Office Action, p.3). The Examiner indicates that "Figure 3 is sufficiently poor enough that it is difficult to determine what is actually being described." (Office Action, p.3-4).

Applicants submit corrected drawing sheets in compliance with 37 CFR 1.21(d) together with this response. Accordingly, Applicants respectfully request that the foregoing rejection be withdrawn.

Claim Rejections

35 USC §112, second paragraph

Claims 20 – 22 and 34 – 36 have been rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. (Office Action, p.5). Applicants respectfully disagree.

The Examiner argues that "(t)he claims are rejected because they recite the term "MINOR" (and) the term "MINOR" is indefinite and the metes and bounds of the claims cannot be determined since abbreviations often have more than one meaning. The Examiner indicates that "(i)nsertion of the full name of the mitogen induced nuclear orphan receptor (MINOR) would overcome the instant rejection." (Office Action, p.5).

Applicants have amended the present claims to recite the full name of the mitogen induced nuclear orphan receptor (MINOR) and respectfully request that the foregoing rejection be withdrawn.

The Examiner also indicates that "claim 36 is rejected because the claim recites, '(a) obtaining dendritic cells from the individual' and '(b) causing the dendritic cells to express the antigen' (and) there is insufficient antecedent basis for these limitation in the claim." (Office Action, p.5).

Applicants have amended claim 34 to recite proper antecedent basis, and note that claim 36 does not recite an individual or an antigen. Applicant's respectfully request that the foregoing rejection be withdrawn.

35 USC §112, first paragraph

Claims 20 – 22, 34 and 35 have been rejected under 35 USC §112, first paragraph, because the specification, while being enabling for a dendrite cell-based vaccine comprising dendritic cells expressing MINOR siRNA comprising SEQ ID NO: 2 and SEQ ID NO: 3 or a population of dendritic cells for use in vaccination of a subject, wherein the population of dendritic cells comprise SEQ ID NO: 2 and SEQ ID NO: 3, does not reasonably provide enablement for a dendrite cell-based vaccine comprising dendritic cells expressing siRNAs having substantial sequence homology to MINOR or a population of dendtritic cells for use in vaccination of a subject, wherein the population of dendritic cells comprise an agent that inhibits MINOR expression." (Office Action, p.5). Applicants respectfully disagree.

The present claims recite a dendritic cell-based vaccine comprising dendritic cells expressing siRNA's having substantial sequence homology to mitogen induced nuclear orphan receptor (MINOR). (Claim 20). The claims also recite "a population of dendritic cells for use in vaccination of a subject produced by the process of (a) obtaining dendritic cells from the individual; (b) causing the dendritic cells to express the antigen by either (i) exposing the dendritic cells to the antigen in culture under conditions promoting uptake and processing of the antigen, or (ii) transfecting the dendritic cells with a gene encoding the antigen; (c) activating the antigen-expressing dendritic cells, (d) treating the dendritic cells with an agent that inhibits mitogen induced nuclear orphan receptor (MINOR) expression, wherein the agent that inhibits MINOR expression is selected from peptides, peptidomimetics, small molecules or inhibitory nucleotides." (Claim 34).

The MPEP states that the determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing a combination of factual considerations: the breath of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples,

and the quantity of experimentation necessary. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. Accordingly, the Examiner has considered these factors in his rejection:

Nature of the Invention and breath of the claims

According to the MPEP at 2164. 05(a), "whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art."

According to the MPEP at § 2164.08 as concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. AK Steel Corp. v. Sollac, 344 F.3d 1234, 1244, 68 USPQ2d 1280, 1287 (Fed. Cir. 2003); In re Moore, 439 F.2d 1232, 1236, 169 USPQ 236, 239 (CCPA 1971).

As to the nature of the invention and breath of the claims, the Examiner alleges that "the broadness of the claims implies a dendrite cell-based vaccine comprising dendritic cells expressing any siRNA having substantial sequence homology to the MINOR gene or any agent that inhibits MINOR expression (and) the nature of the invention, therefore, requires the knowledge of using dendrite vaccines in a subject." (Office Action, p.6).

As discussed in the specification, DC-based vaccines have been tested in a number of animal models, and have also been translated to clinical medicine in several trials. The specification, at p. 3, discusses two primary methods that have been used in the art to produce DC based vaccines. Giboa et al. (J Clinical Investig. 2007; attached herein), discusses DC based vaccines, and in particular, advances that have been made in immunizing cancer patients with autologous, patient-derived DCs loaded with tumor antigens ex vivo. As Gilboa describe, although the field is marked with certain hurdles,

clear progress has been made in advancing DC based vaccines. Clearly, DC based vaccines were known to one of skill in the art at the time of filing.

Applicants argue that in view of the present claims, and given the disclosure and working examples, and what was known in the art at the time of filing, the nature of the invention is enabled as claimed.

Amount of direction or guidance and presence/absence of working examples

According to the MPEP at § 2164.03, the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

According to the MPEP at § 2164.02, compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or "prophetic." A working example is based on work actually performed. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.

As to the working examples, the Examiner argues that "the specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to make a dendrite cell-based vaccine comprising dendritic cells expressing any siRNA having substantial sequence homology to MINOR (and) a person skilled in the art would recognize that the use of dendritic-based vaccines is unpredictable." (Office Action, p.7). Applicants disagree.

Making (or buying commercially available pre-made constructs) and using siRNA was well known to one of skill in the art at the time of filing. Moreover, Applicants provide ample teaching in the specification about small interfering RNA technology. For example, at p. 30, Applicants teach the state of the art of siRNA technology at the time of filing:

> Recently, techniques have been developed to trigger RNA interference (RNAi) against specific targets in mammalian cells by introducing exogenously produced or intracellularly expressed siRNAs (Elbashir, 2001; Brummelkamp, 2002). These methods have proven to be quick, inexpensive and effective for knockdown experiments in vitro and in vivo (2 Elbashir, 2001; Brummelkamp, 2002; McCaffrey, 2002; Xia, 2002). The ability to accomplish selective gene silencing now allows the use of siRNAs to suppress gene expression for therapeutic benefit (Xia, 2002; Jacque, 2002; Gitlin, 2002). In the context of the present invention, siRNAs have been developed which prevent or inhibit the expression of the MINOR gene in dendritic cells, potentiating the lifespans of siRNA treated dendritic cells, and thereby increasing their immunogenicity.

Further, Applicants teach what is meant by siRNA silencing, where:

> As used herein the term "substantial silencing" means that the mRNA of the targeted MINOR allele is inhibited and/or degraded by the presence of the introduced siRNA, such that expression of the targeted allele is reduced by about 10% to 100% as compared to the level of expression seen when the siRNA is not present. Generally, when an allele is substantially silenced, it will have at least 40%, 50%, 60%, to 70%, e.g., 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, to 79%, generally at least 80%, e.g., 81%-84%, at least 85%, e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or even 100% reduction expression as compared to when the siRNA is not present. As used herein the term "substantially normal activity" means the level of expression of an allele when an siRNA has not been introduced to a dendritic cell. It should be noted that others forms of anti-sense technology are included as embodiments of the present invention to inhibit MINOR gene expression in dendritic cells.

Accordingly, a skilled artisan is enabled to make a dendrite cell-based vaccine comprising dendritic cells expressing any siRNA having substantial sequence homology to MINOR based on the teaching in the specification and the knowledge in the art at the time of filing.

The state of the prior art and the predictability or unpredictability of the art

According to the MPEP at 2164. 05(a), "(t)he state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains (and) the state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date."

As to the state of the art and the level of predictability in the art the Examiner alleges that "Applicant and the art has shown a high level of unpredictability regarding dendrite cell-based vaccines, including those DC based vaccines comprising an agent that inhibits MINOR." (Office Action, p.8). The Examiner cites the Wang reference (Blood, 2009) and argues that "the art of Wang also teach that mice vaccinated with DCs expressing MNOR siRNA ultimately died, and there was no significant difference in long term survival, however inhibition of MINOR expression in DC vaccines lead to a significant delay in tumor progression." (Office Action, p.8). The Examiner cites the Hermans reference to argue that "although dendritic cells are critical for initiating immune responses, they are relatively short lived in vitro and in vivo and their transience affects their potential for therapeutic use." (Office Action, p.8).

In the present Application, Applicants have identified genes that were selectively upregulated in mature DCs relative to activated macrophages. In Example 1, beginning on p. 34, Applicants describe a subtractive hybridization study used to identify new genes that were specifically upregulated in mature DCs as compared to less potent APCs

(macrophages) and, thus, might contribute to the unique function of these cells. Applicants identify MINOR expression to be quite selective for DCs. (p.35). Applicants confirm the relative expression levels of MINOR between DCs and activated macrophages using quantitative PCR. (p.35). Applicants teach that constitutive MINOR expression induces cell death (Example 5). Further, Applicants describe generation of a lentivirus-based vector expressing siRNA to genetically suppress MINOR expression in Example 6 beginning on p. 39. Applicants generate six different siRNAs corresponding to the Nor-1 gene (rat MINOR GenBank accession no. NM--015743) and construct lentivirus based siRNA constructs that decrease the expression of MINOR. Applicants then test whether the siRNA-MINOR would inhibit cell death in primary BM-derived cultures by generating BM-DCs and determining natural apoptosis. (Example 8, p. 41). Since it appeared that transduction with siRNA-MINOR could inhibit cell death, it was hypothesized that it would also enhance the immunogenicity of BM-DCs when used as a vaccine. Accordingly, to assess the immunogenicity of ex vivo-generated, HA-pulsed DCs, DCs were generated from BM, transduced with either GFP or siRNA-MINOR GFP, and pulsed with the class II restricted peptide for HA (see Figure 10). Figure 10 shows siRNA-MINOR transduction of ex vivo-generated, HA-pulsed DCs enhances their immunogenicity. Applicants further show that activation of DCs leads to upregulation of MINOR in vivo (see, e.g. Example 12). Finally, in order to address the relevance of these findings to the clinical setting, namely, inhibiting MINOR in ex vivo DC vaccines, human DC MINOR expression patterns were described (Example 17). Applicants show that there is a dramatic upregulation of MINOR in activated DCs, as previously found in the murine system. All of the Applicants data and teaching, taken together, does not support the Examiner's argument that Applicant has shown a high level of unpredictability regarding dendrite cell-based vaccines, including those DC based vaccines comprising an agent that inhibits MINOR.

Regarding DC based vaccines, Giboa (2007, above) discusses advances that have been made in DC vaccine research to address the maturation of DC's, including optimizing the ex vivo DC maturation process and maturing the DCs in situ. Giboa (2007) discuss multiple clinical trials that have been carried out targeting different cancers using different

methods of generating DCs, different antigens, and different antigen-loading techniques. Giboa discusses failures and successes of DC vaccine trials, where and how the cells are frozen and thawed, how long the cells are matured, at what speed they are centrifuged, the mechanics of their administration, and the time intervals between boostings can have a critical impact on the outcome of the treatment. Giboa discuss the successful trial of Andrieu et al. who showed that, first in rhesus macaques infected with SIV and subsequently in patients chronically infected with HIV, that DC vaccination induced robust T cell responses in most vaccines and that this correlated with marked reduction in viral titers. (p.1201). Further, even in 1998 (Cancer Immunol Immunother. 1998 Apr;46(2):82-7; abstract provided herein), Giboa et al. reported on immunotherapy of cancer with dendritic-cell-based vaccines. Giboa teach that animal studies demonstrated that vaccination with genetically modified tumor cells or with dendritic cells (DC) pulsed with tumor antigens are potent strategies to elicit protective immunity in tumor-bearing animals, more potent than "conventional" strategies that have been tested in clinical settings with limited success. While both vaccination strategies are forms of cell therapy requiring complex and costly ex vivo manipulations of the patient's cells, current protocols using dendritic cells are considerably simpler and would be more widely available.

Accordingly, Applicants have provided ample evidence that dendrite cell-based vaccines, including those DC based vaccines comprising an agent that inhibits MINOR, as instantly claimed are enabled by the instant disclosure.

The level of skill in the art

According to the MPEP at § 2164.05(b), the relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. Where different arts are involved in the invention, the specification is enabling if it enables persons skilled in each art to carry out the aspect of the invention applicable to their specialty. In re Naquin, 398 F.2d 863, 866, 158 USPQ 317, 319 (CCPA 1968).

As to the level of one of ordinary skill in the art, the Examiner argues that "the relative skill of those in the art is considered to be high, being a graduate student or post-doctoral fellow in a biological science." (Office Action, p.9).

Applicants submit that the specification enables persons skilled in each art to carry out the claims as applicable to their specialty.

The quantity of experimentation necessary

The Examiner argues that "(i)n order to practice the invention using the specification and the state of the art as outlined above, the quantity of experimentation required to practice the invention as claimed would require the de novo determination of those population of dendrites expression MINOR siRNA that are successfully used as dendrite-based vaccinations against cancer, viral disease, bacterial disease or immune disorders." (Office Action, p.10). The Examiner argues that "since the specification fails to provide any real guidance for a dendritic cell vaccine...other than SEQ ID NO: 2 and SEQ ID NO: 3, and since resolution of the various complications in regards to using dendritic-based vaccines is unpredictable, one of skill in the art would have been unable to practice the invention, commensurate in scope with the claims, without engaging in undue trial and error experimentation." (Office Action, p.10).

For the reasons discussed above, Applicants submit that there is ample guidance and working example in the specification, the level of unpredictability in the art is not high, and the breath of the given claims is commensurate with the scope of protection sought by the claims, such that undue experimentation is not required to practice the full scope of the claims.

Applicants respectfully request that the rejection be reconsidered and withdrawn.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: October 8, 2010

Respectfully submitted,

Electronic signature: /Peter F. Corless/
Peter F. Corless
Registration No.: 33,860
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 517-5557
Attorneys/Agents For Applicant